Remarks

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

By this amendment, new claims 55-60 have been introduced. Descriptive support for these claims is provided at page 15, line 25 to page 16, line 13.

The rejection of claims 1-5 and 43-54 under 35 U.S.C. § 112 (2nd para.) for indefiniteness is respectfully traversed.

It is the position of the U.S. Patent and Trademark Office ("PTO") that the use of the term "constituents" in relation to a heparin fraction renders claims 1-5 and 43-54 indefinite. In view of the above amendments which have deleted this term, this rejection is respectfully traversed.

With respect to claims 43 and 54, it is the position of the PTO that the terms "derivatives" and "analogs", respectively, are relative terms and that in the absence of specific examples, render the claims indefinite. Applicant respectfully disagrees.

With respect to claim 43, the present invention recites several examples of suitable heparin "derivatives" as well as methods of synthesizing them. Specifically, "Heparin derivatives can be obtained by deaminating hydrolysis of unfractionated heparin...with formation of di-, tetra-, hexa, and higher saccharides terminated with 2, 5-anhydro-D-mannose(AM) residues..." (page 19, lines 11-15). The present application further recites that suitable heparin derivatives are described "...for example, in Kosakai et al., *J. Biochem.*, 83:1567-75 (1978); Braswell, *Biochim. Biophys. Acta*, 158:103-106 (1968); Fransson et al., *FEBS Lett.*, 97:119-23 (1979); Nagasawa et al., *Meth. Carbohydrate Chem.*, VIII:291-4 (1980); Liu et al., *J. Pharm. Sci.*, 83:1034-1039 (1984)..." which were incorporated by reference in their entirety and describe with specificity numerous derivatives of heparin (page 19, lines 26-31). The PTO is respectfully reminded that while "...the naming of one member of ... a group is not, in itself, a proper basis for a claim to the entire group... it may not be necessary to enumerate a plurality of species if the genus is sufficiently identified in an application by 'other appropriate language'" (119 F.3d 1559 (Fed. Circ. 1997)). In the present application, it is apparent that numerous derivatives of heparin are sufficiently identified, directly and indirectly, thus the rejection of claim 43 for indefiniteness is improper and should be withdrawn.

With respect to claim 54, contrary to the position of the PTO the term "analog" is not indefinite. One skilled in the art, i.e., a biochemist or physician conducting

research on treatments for angiogenesis-mediated disorders, would understand the term analog to encompass chemical molecules which differ only by the transposition of one atom or a simple functional group for another, i.e., replacing bromine with iodine, or a hydrogen with a methyl group. Accordingly, folate, purine, adenosine, and pyrimidine analogs, as recited in claim 54, would differ from their respective base molecule by a simple transposition of a single atom or functional group for another. Therefore, one skilled in the art would have had no difficulty ascertaining which compounds were encompassed by the term "analog". Thus, the rejection of claim 54 for indefiniteness is improper and should be withdrawn.

The rejection of claims 1-5 and 43-54 under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 4,963,580 to Mascellani et al. ("Mascellani") in view of U.S. Patent No. 5,908,837 to Cohen et al. ("Cohen") is respectfully traversed.

Mascellini teaches oxidized heparin fractions with a molecular weight ranging between 2,000 and 7,000 daltons having high antithrombic activity, poor or no anticoagulant activity, and anti-inflammatory activity. Mascellini does not disclose a heparin fraction in which anticoagulant activity has been substantially eliminated nor a heparin fraction in which the hydroxyl residues are oxidized in an amount sufficient to substantially eliminate anticoagulant activity. In addition, Mascellini does not teach compositions containing such a heparin fraction in combination with a non-heparin agent or drug.

Cohen teaches oxidized heparin fractions with a molecular weight between 3,000 and 6,000 daltons in a pharmaceutical composition with non-heparin angiogenic inhibitors. Cohen does not disclose a heparin fraction in which anticoagulant activity has been substantially eliminated nor a heparin fraction in which the hydroxyl residues are oxidized in an amount sufficient to substantially eliminate anticoagulant activity.

It is the position of the PTO that it would have been obvious to one skilled in the art to select oxidized heparin fractions having high antithrombic activity and poor or no anticoagulant activity, as taught by Mascellini, for use in a pharmaceutical composition containing non-heparin angiogenic inhibitors, as taught by Cohen, to obtain the present invention. Applicant respectfully disagrees.

According to the present invention, low and/or ultra-low molecular weight heparin ("LMWH") fractions possessing substantially no anticoagulant activity were produced. This was achieved by oxidizing the hydroxyl residues of a fraction in an amount sufficient to substantially eliminate anticoagulant activity in that fraction. Specifically, the

oxidation of hydroxyl residues was performed to an extent which substantially eliminated *both* antithrombin (AT) and heparin Co-factor II binding (HCII). Both AT and HCII binding of heparin are known to be responsible for heparin-associated anti-coagulant activity (O'Keeffe et al., "The Heparin Binding Properties of Heparin Cofactor II Suggest an Antithrombin-like Activation Mechanism", 279:50267-50273 (2004); Spencer et al., "Novel Inhibitors of Factor X for Use in Cardiovascular Diseases", *Curr. Cardiol. Rep.* 2:395-404 (2000); Gustafsson et al., "Oral Direct Thrombin Inhibitors in Clinical Development", *J. Intern. Med.* 254:322-334 (2003)). Therefore, because anti-coagulant activity was substantially eliminated in LMWH fractions, as shown in Tables 1 and 2, the fractions were devoid of both AT and HCII binding. This is unlike other oxidized LMWHs which still maintain HCII binding, indicating at least some persisting anticoagulant effects.

Indeed, Mascellini does not teach or suggest a heparin fraction in which anticoagulant activity has been substantially eliminated, nor a heparin fraction in which the hydroxyl residues are oxidized in an amount sufficient to substantially eliminate anticoagulant activity.

Therefore, it would not have been obvious to one skilled in the art to look to Mascellini for guidance in producing LMWH fractions possessing substantially no anticoagulant activity, as recited in claims 1-5 of the present invention.

With respect to claims 43-54, because Mascellini would not have motivated one skilled in the art to produce LMWH fractions possessing substantially no anticoagulant activity, in which the fraction was oxidized in an amount sufficient to substantially eliminate anticoagulant activity, it would not have been obvious to use those heparin fractions in a composition with standard heparin, heparin derivatives, or non-heparin anti-coagulants, as recited in claims 43-54.

Cohen does not remedy the deficiencies of Mascellini. Cohen discloses a LWMH fraction in a pharmaceutical composition with non-heparin angiogenic inhibitors. No where does Cohen teach or suggest a low molecular weight heparin fraction possessing substantially no anticoagulant activity.

For these reasons, neither Cohen nor Mascellini, either alone or in combination, would have motivated one skilled in the art to employ a LMWH fraction having substantially no anticoagulant activity, in which the hydroxyl residues of the fraction were oxidized to an extent which substantially eliminated anticoagulant activity of that fraction, in a composition as presently claimed.

Therefore, the rejection of claims 1-5 and 43-54 for obviousness over Mascellani in view of Cohen is improper and should be withdrawn.

In view of all of the foregoing, applicant submits that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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